Acta Medica Okayama

Volume 37, *Issue* 6 1983 *Article* 7

DECEMBER 1983

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Abstract

Using the ventriculo-cisternal perfusion method, the effects of droperidol and ketamine hydrochloride on cerebrospinal fluid (CSF) production were studied in dogs. Neither droperidol (0.25 mg/kg, IV) nor ketamine (3 mg/kg, IV) caused a statistically significant change in CSF production rate. Positive correlation between CSF production and corresponding cerebral perfusion pressure (CPP) was observed in the ketamine study, whose unfavorable effect on neurosurgical anaesthesia would be obvious. On the other hand droperidol (0.25 mg/kg, IV) tended to decrease CSF production. Droperidol alone or in combination with other analgesics such as fentanyl as currently used in neurosurgical anaesthesia appears to be an appropriate choice in patients with increased intracranial pressure.

KEYWORDS: cerebrospinal fluid production, ketamine, droperidol

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*PMID: 6666678 [PubMed - indexed for MEDLINE]

Acta Med. Okayama 37, (6), 511-517 (1983)

FAILURE OF DROPERIDOL AND KETAMINE TO INFLUENCE CEREBROSPINAL FLUID PRODUCTION IN THE DOG

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Received September 28, 1983

Abstract. Using the ventriculo-cisternal perfusion method, the effects of droperidol and ketamine hydrochloride on cerebrospinal fluid (CSF) production were studied in dogs. Neither droperidol (0.25 mg/kg, IV) nor ketamine (3 mg/kg, IV) caused a statistically significant change in CSF production rate. Positive correlation between CSF production and corresponding cerebral perfusion pressure (CPP) was observed in the ketamine study, whose unfavorable effect on neurosurgical anaesthesia would be obvious. On the other hand droperidol (0.25 mg/kg, IV) tended to decrease CSF production. Droperidol alone or in combination with other analgesics such as fentanyl as currently used in neurosurgical anaesthesia appears to be an appropriate choice in patients with increased intracranial pressure.

Key words : Cerebrospinal fluid production, ketamine, droperidol.

Although the effect of anaesthetic agents on cerebrospinal fluid (CSF) pressure have been extensively studied, anaesthetic agents have not been investigated as to their influence on the volume of CSF formation. Additional knowledge of the effect of anaesthesia on CSF production may influence the selection of anaesthetic agents for surgery.

This study was performed to investigate the effect of droperidol and ketamine hydrochloride on the rate of CSF production in the dog.

METHODS

Thirteen mongrel dogs weighing from 11.0 to 24.2 kg (mean 14.0 kg) were used for this study. Seven dogs were used for the ketamine study and six dogs for the droperidol study. Anaesthesia was induced with intravenous chloralose 80 mg/kg. After endotracheal intubation the lungs were mechanically ventilated with a Harvard Animal Ventilator (Model 607) with a mixture of oxygen and nitrogen. End-tidal CO^2 concentration was continuously monitored with a Beckman LB-2 Medical Gas Analyzer and min volume was regulated to maintain alveolar CO_2 between 5 to 5.5 %. Arterial pO_2, pCO_2 and pH were measured every 30 min during the experiments. Inspired oxygen concentration was adjusted to maintain the paO_2 between 13.3 and 20 kPa. A femoral artery and vein were cannulated for arterial pressure determination and venous access for continuous intravenous infusion and blood samples. Lactated Ringer's solution was infused intravenously throughout the procedure. The amount of fluid infused was limited to the estimated blood loss associated with the surgical procedure

and blood sampling. Arterial blood pressure was monitored with a Statham pressure transducer. Lead II of EKG was also recorded. Body temperature was maintained at approximately 37 ℃ with a radiant heating lamp. Ventriculo-cisternal perfusion was carried out by the technique originally reported by Pappenheimer and his associates for the measurement of CSF production (1, 2).

The left lateral ventricle was cannulated with a 21 gauge scalp vein infusion set through a 9 mm trephine hole placed in the parietal bone 1 cm posterior to the coronal suture and 1.5 cm lateral to the sagittal suture on both sides of the midline. Through a cervical laminectomy a radiopaque plastic cannula was passed cephalad in the subarachnoid space to the cisterna magna. The position of the catheter was confirmed by X-ray. Another 9 mm trephine hole was drilled in the midline of the skull to expose the sagittal sinus. The sagittal sinus pressure was measured by a plastic catheter and referred to the level of the heart as the zero point. During these experimental preparations, which usually lasted one h, chloralose anaesthesia was supplemented with 0.5 % xylocaine infiltration for the performance of the trephines and the cervical laminectomy.

Artificial CSF containing inulin (100 mg/l) as an indicator was introduced into the lateral ventricle by a Harvard infusion pump (Series 940, 2 channel, parallel/reciprocal) utilizing a calibrated 50 ml glass syringe. CSF was withdrawn from sisterna magna by the same Harvard pump.

The artificial CSF contained Na 149.5 mmol/l, K 3.5 mmol/l, Mg 0.4 mmol/l, Ca 0.33 mmol/l, Cl 129 mmol/l, H_2PO_4 0.16 mmol/l, HCO_3 12.5 mmol/l and inulin 100 mg/l. pH of CSF was adjusted to 7.4 by bubbling CO_2 thru the solution prior to perfusion. One h of artificial CSF infusion from the lateral ventricle to the cisterna magna preceded the 90 min experimental period. The initial infusion rate was rapid to equilibrate the artificial CSF with the endogenous CSF in the ventricles. After control samples were obtained either ketamine (3 mg/kg) or droperidol (0.25 mg/kg) were administered intravenously. CSF collection periods of 15 min each were utilized during the 90 min study period. The concentration of inulin in CSF was measured by the resorcinol method (3).

Volume of CSF production was calculated as follows :

$V_F = V_I (C_I - C_0)/C_0$

Where : V_F = volume of formed CSF V_I = rate of infusion (ml/min)

C_I = inulin concentration at inflow C_0 = inulin concentration at outflow

Cerebral perfusion pressure (CPP) was calculated from the mean arterial blood pressure and the cerebral venous pressure obtained from the superior sagittal sinus (CPP = mean arterial blood pressure-cerebral venous pressure).

RESULTS

Table 1 has the observed values for cerebrospinal fluid production and the associated cerebral perfusion pressure (CPP). All values are shown as mean ± S.E. Correlation coefficient was calculated. The date was evaluated using the Student's t-test. If $P < 0.05$ the changes were considered significant. Each CSF production rate was plotted against the corresponding CPP (Fig. 1). CSF production rate (μl/min/kg) and perfusion pressure during the 90 min study period are shown in Figs. 2 and 3.

Our control values of CSF production rate are in agreement with the previous-

TABLE 1. CEREBROSPINAL FLUID PRODUCTION RATE AND CEREBRAL PERFUSION PRESSURE

	Period studied (min)						
	0	15	30	45	60	75	90
Ketamine							
CSF (μl/min/kg)	3.1±0.7	3.1±1.1	3.2±0.8	2.8±1.0	2.4±0.6	3.2±0.9	3.3±0.7
CPP (kPa)	15.5±0.9	14.8±0.9	15.5±1.1	14.9±1.3	15.5±1.6	13.9±2.0	14.9±1.6
Droperidol							
CSF (μl/min/kg)	4.4±2.0	3.2±1.3	2.7±1.0	3.1±0.9	3.4±1.1	3.2±0.9	3.9±1.5
CPP (kPa)	14.8±1.5	12.0±1.1*	11.1±0.9*	9.5±1.5*	10.8±1.6*	11.2±0.9*	11.7±0.9*

CSF: Cerebrospinal fluid production. CPP: Cerebral perfusion pressure Valves are expressed as mean I standard error. * shows statistically significant difference by the Students t-test.

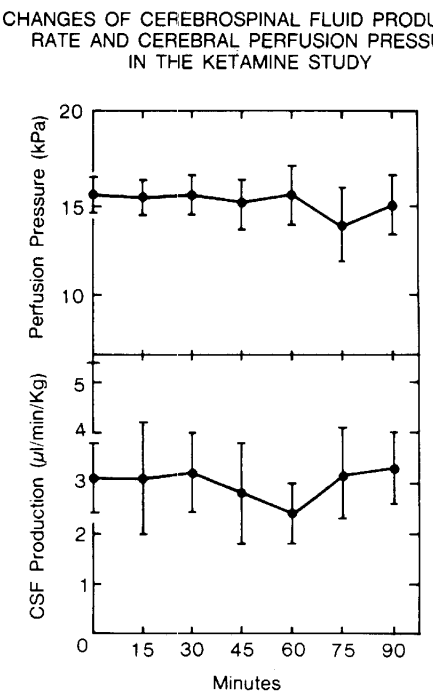

Fig. 1. Each CSF production rate was plotted against the corresponding CPP. In the ketamine group, CSF production (μl/min/kg) = 0.20 × cerebral perfusion pressure (kPa) + 0.82. In the droperidol group, CSF production rate was not correlated with the level of CPP.

ly reported values (4-7). Following 0.25 mg/kg droperidol, CSF production decreased to 61 % of control value at 30 min, then gradually increased, but did not return to the control value at 90 min. CSF production rate was not correlated with the level of the CPP. ($n = 42$, $r = 0.08055$, $p > 0.05$). Only the decrease

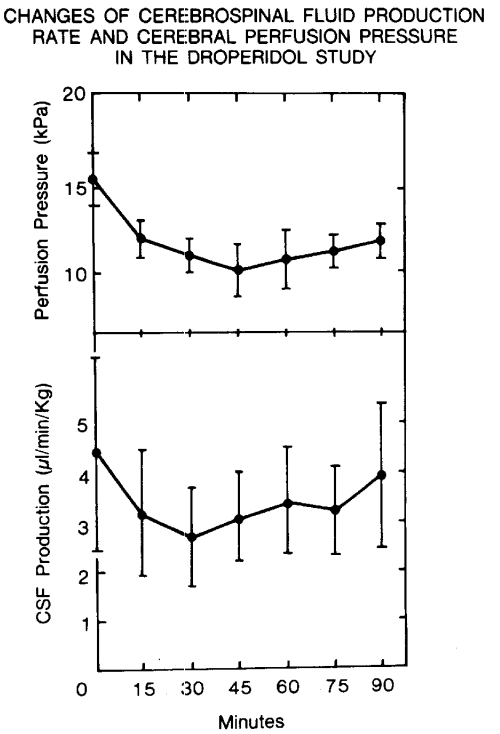

Fig. 2. Responses of cerebrospinal fluid production and cerebral perfusion pressure to droperidol (0.25 mg/kg) administration.

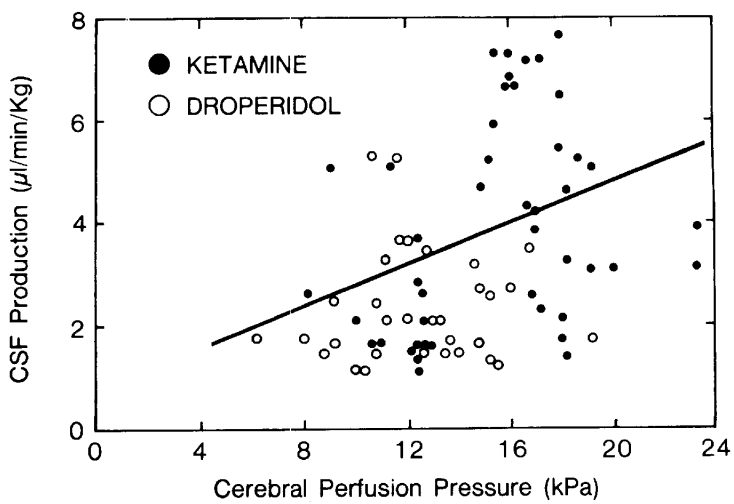

Fig. 3. Responses of cerebrospinal fluid production and cerebral perfusion pressure to ketamine (3 mg/kg) administration.

in CPP was statistically significant (Fig. 2).

In the ketamine group the CPP and CSF production changes were not statistically significant (Fig. 3). However, CSF production rate was correlated with CPP ($n = 49$, $r = 0.322$ $p < 0.05$).

DISCUSSION

Physiological factors which may influence CSF production include arterial pH, pO_2 and pCO_2 (8-12) temperature (13, 14), arterial blood pressure (15) and CSF pressure (1, 2, 6, 7, 16-27).

In this study body temperature and arterial pCO_2 and pO_2 were maintained within normal limits. Arterial blood pressure, $CMRO_2$ and CSF pressure were altered by the drugs being studied.

Bering reported that CSF production was statistically and significantly correlated with $CMRO_2$ (5). His results could also explain the difference seen in the droperidol and ketamine group. Ketamine has been reported to increase $CMRO_2$ (22). Droperidol has little effect on $CMRO_2$ (23).

In the droperidol study CSF production rate was not associated with a change in cerebral perfusion pressure (Fig. 1). However, positive correlation between CSF production and CPP was observed in the ketamine study. A decreased rate of CSF production with increased CSF pressure was reported in the rabbit and cats by Sahar and his associates (17, 19, 20). While others (2, 6, 16, 18) reported that CSF pressure changes had little or no significant effect on CSF production. Several factors, such as species differences, the use of anaesthetized versus non-anaesthetized animals, or alterations in perfusion pressure, may be responsible for their conflicting results. However, there is no report that an increased CSF pressure or perfusion pressure increases CSF production. Reasons for this observation remain to be solved.

A potential source of error in the experiment is the time required to equilibrate artificial CSF with a dog's CSF. Artificial CSF must be infused until the ventriculocisternal system is equilibrated with an artifical CSF before a measurement is started. Halliday and Moir (21) reported that it took up to 1.5 h for the CSF system to become fully equilibrated with the perfusion fluid. They used beagle dogs weighing 12 to 16 kg with an infusion rate of 300 ul/min. Mean body weights of their dogs were not reported. The body weight of their animals is probably comparable to that of the present study. The infusion rate used in this study was 382 ul/min. This faster infusion rate could compensate the difference in infusion time and reduce equilibration time. However, the irregularity of the equilibration time might be a cause of the wider variation seen in the observed values of the study.

Droperidol in a combination with fentanyl is currently a method of management in neuroanaesthesia practice, especially in the management of patients with increased intracranial pressure. The decrease in CPP and the minimal changes

in the volume of CMS production observed in the droperidol study would support its usage in the presence of increased intracranial pressure. Ketamine is considered to be contraindicated in these patients because of it's previously reported deleterious effect on CSF pressure and CPP changes. Positive correlation between CSF production rate and CPP shown in Fig. 1 would further substantiate that ketamine is an unfavorable choice of the anaesthetic agent in the neurosurgical anaesthesia.

Acknowledgments. Thsi study was supported by USPHS Basic Research Support Grant 383.

REFERENCES

1. Pappenheimer, J.R., Heisey, S.R. and Jodan, E.F.: Perfusion of the cerebral ventricular system in unaesthetized goats. *Am. J. Physiol.* **203,** 763-774, 1962.
2. Heisey, S.R., Held, D. and Pappenheimer, J.R.: Bulk flow and diffusion in the cerebrospinal fluid system of the goat. *Am. J. Physiol.* **203,** 775-781, 1962.
3. Schreiner, G.E.: Determination of inulin by means of resorcinol. *Proc. Soc. Exp. Biol Med.* **74,** 117-120. 1950.
4. Oppelt, W.W., Patlak, C.S. and Rall, D.P.: Effect of certain drugs on cerebraspinal fluid production in the dog. *Am. J. Physiol.* **206,** 247-250, 1964.
5. Bering, E.A.: Cerebrospinal fluid production and its relationship to cerebral metabolism and cerebral blood flow. *Am. J. Physiol.* **197,** 825-828, 1959.
6. Bering, E.A. and Sato, O.: Hydrocephalus : Changes in formation and absorption of cerebrospinal fluid within the cerebral ventricles. *J. Neurosurg.* **20,** 1050-1063, 1963.
7. Sato, O., Bering, E.A., Yagi, M., Tsugane, R., Hara, H., Amano, Y. and Asai, T.: Bulk flow in the cerebrospinal fluid system of the dog. *Acta Neurol. Scand.* **51,** 1-11, 1975.
8. Ames, A., Higashi, K. and Nesbett, F.B.: Effects of pCO_2, acetzaolamide and oubain on volume and composition of chroid plexus fluid. *J. Physiol.* **181,** 516-524, 1965.
9. Hochwald, G.M., Malhan. C. and Brown, J.: Effects of hypercapnia on CSF turnover and blood-CSF barrier to protein. *Arch. Neurol.* **28,** 150-155, 1973.
10. Holloway, L.S. and Cassin, S.: Cerebrospinal fluid dynamics in the newborn dog during nomoxia and hypoxia. *Am. J. Physiol.* **223,** 499-502, 1972.
11. Michael, D.K. and Heisey, S.R.: Effects of brain ventricular perfusion and hypoxia on CSF formation and absorption. *Exp. Neurol.* **41,** 769-772, 1973.
12. Oppelt, W.W., Maren, T.H., Owens, E.S. and Rall, D.P.: Effects of acid base alterations on cerebrospinal fluid production. *Proc. Soc. Exp. Biol. Med.* **114,** 86-89, 1963.
13. Davson, H. and Spaziani, E.: Effect of hypothermia on certain aspects of the cerebrospinal fluid. *Exp. Neurol.* **6,** 118-128, 1962.
14. Snodgrass, R. and Lorenzo, A.V.: Temperature and cerebrospinal fluid production rate. *Am. J. Physiol.* **222,** 1524-1527, 1972.
15. Carey, M.E. and Vela, A.R.: Effect of systemic arterial hypotension on the rate of CSF formation in dogs. *J. Neurosurg.* **41,** 350-355, 1974.
16. Cutler, P.W.P., Page, L., Galicicl, I. and Watters, G.W.: Formation and absorption of cerebrospinal fluid in man. *Brain* **91,** 707-720, 1968.
17. Hochwald, G.M. and Sahar, A.: Effect of spinal fluid pressure on cerebrospinal fluid formation. *Exp. Neurol.* **32,** 30-40, 1971.
18. Rubin, R.C., Henderson, E.S., Ommaga, A.K., Waler, M.D. and Rall, D.P.: The production

of cerebrospinal fluid in man and its modification by acetazolamide. *J. Neurosurg.* **25,** 430-436, 1966.

19. Sahar, A., Hochwald, G.M. and Ransohoff, J.: Experimental hydrocephalus : Cerebrospinal fluid formation and ventricular size as a function of intraventricular pressure. *J. Neurol. Sci.* **11,** 81-91, 1970.
20. Sahar, A.: The effect of pressure on the production of cerebrospinal fluid by the choroid plexus. *J. Neurol. Sci.* **16,** 49-58, 1972.
21. Halliday, J. and Moir, A.T.: The effects of certain anaesthetic and an icnvulsant drugs on the CSF pottassium fluxes of the dog. *Br. J. Pharmacol.* **52,** 27-34, 1974.
22. Dawson, B., Michenfelder, J.D. and Theye, R.A.: Effects of ketamine on canine cerebral blood flow and metabolism ; modification by prior administration of thiopental. *Anesth. Analg.* **50,** 1971. 443-447,
23. Michenfelder, J.D. and Theye, R.A.: Effects of fentanyl, droperidol and Innovar on canine cerebral metabolism and blood flow. *Br. J. Anaesth.* **43,** 630-636, 1971.